anhydrase, respectively, as 21.5kD and 31kD molecular weight standards and comprises the amino acid sequence of SEQ ID NO.: 1, or a complement of said nucleic acid molecule.

80. (New) An isolated nucleic acid molecule encoding OMP21 protein, wherein said nucleic acid molecule comprises a sequence selected from the group consisting of:

a) a nucleic acid sequence of SEQ ID NO: 6;

b) a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 7; and

c) a nucleic acid sequence which hybridizes at 68 degrees C in 0.5M NaHPO4 (pH7.2)/1 mM EDTA/ 7% SDS to any one of the sequences of a) or b); and encodes a polypeptide that elicits an immune response to *M. catarrhalis* when administered to an animal;

or a complement of said nucleic acid molecule.

81. (New) The isolated nucleic acid of Claim 9, which comprises the nucleic acid sequence of SEQ ID NO.: 6.

82. (New) An isolated nucleic acid molecule encoding a fragment of OMP21, said fragment comprising the amino acid sequence of SEQ ID NO.: 1.

## REMARKS

Upon entry of the present amendments, Claims 9, 11-13, 16, 20, 71-73 and 75-82 will be pending and under active consideration. Claim 74 is canceled, without prejudice, and new Claims 79-82 are added by amendment herein. No new matter is added.

Applicants gratefully acknowledge the indication, at page 11 of the Office Action, that Claims 9, 11-13, 16, 20 and 71-78 are free of the prior art of record.

## Objections/Rejections

The specification is objected to under 35 U.S.C. §1.132 as allegedly containing new matter in the recitation of "99878" on page 66 as the accession number of the microorganism deposited with the ATCC. In addition, Claim 12 is rejected under 35 U.S.C. §112, 1st paragraph as containing new matter as not described at the time of filing with respect to the recited accession number and as non-enabled with regard to the deposited microorganism since it is not clear all Budapest Treaty requirements are met regarding the deposit.

Attorneys for Applicants respectfully disagree and submit herewith a Declaration Regarding the Deposited Microorganism by Dr. W. James Jackson (Jackson Declaration) with attached Exhibit A on behalf of the Assignee of this application.

Attached to the Jackson Declaration as Exhibit A is a copy of the ATCC Receipt in the case of a deposit under the Budapest Treaty regarding the deposit of plasmid pOMP21X in *E.coli* ToP10 F' made on September 16, 1998, i.e., prior to the filing date of the present application. The attached Receipt indicates that the deposit was viable and assigned ATCC No. 98878. Plasmid pOMP21X is described in the application in Example 9 at pages 60-61. The Jackson Declaration and its attached Exhibit A evidence that the deposited microorganism meets all the Budapest requirements regarding availability, etc. By amendment, in response to the previous Office Action, the specification has been amended to recite the accession number. The remaining required information regarding the deposit is recited in the specification as filed at page 66, lines 1-12. In light of such evidence, it is submitted that amendment of the specification and claims to recite the ATCC accession No. assigned to the deposit does not constitute new matter. See In re Lundak, 773 F.2d 1216 (Fed. Cir. 1985).

Hence, this objection to the specification and the rejections of Claim 12 are avoided and must be withdrawn.

Claims 9 and 11 are objected to for a number of informalities. The term "apparent molecular weight" is objected to as is the use of the term "deduced" with respect to the specific amino acid sequences.

Since these informalities do not affect the patentability or the scope of the claims in any way at all, the claims have been amended to avoid the alleged informalities. Hence, this objection must be withdrawn.

Claims 9, 11, 13, 16, 20 and 71-78 are rejected under Section 112, 1st paragraph as allegedly not meeting the written description requirements. The Office Action alleges that, since Claims 9 and 11 are not limited to nucleic acids encoding an OMP21 protein "obtained from *Moraxella catarrhalis*", the subject matter of such claims is not described sufficiently in the specification.

Attorney's for Applicants do not agree, however, in order to advance prosecution and obtain coverage for certain embodiments of the invention, Claims 9 and 11 (and claims independent thereon) have been amended and new Claims 79-82 have been added to point out and more distinctively claim certain subject matter of the invention.

As amended, Claim 9 (and Claims 13, 16, 20, 71-73, 75-77 and new claim 81 to the extent dependent thereon) recites an isolated nucleic acid encoding an OMP21 protein "wherein said OMP21 protein comprises the amino acid sequence of SEQ ID NO.: 7" or a a full complement of said nucleic acid molecule. Attention is directed to the teaching of the specification as a whole and to page 4, line 24 through page 5, line 3, to Section 5.7 at pages 36-40 entitled "Nucleic Acid Encoding OMP21", and to Example Section 8 at page 57-60. More particularly, attention is directed to page 36, lines 30-36 of the specification and to

Figure 3 (SEQ ID NO.: 6) and Figure 4 (SEQ ID NO.: 7). As stated at page 36 and illustrated in Figure 3, the "present invention... provides nucleic acids encoding OMP21. The nucleotide sequence comprising the entire OMP21 open reading frame is depicted in Figure 3". Further, the specification states that the "amino acid sequence encoded by the open reading of OMP21 is depicted in Figure 4 and SEQ ID NO.: 7". The isolation of the nucleic acid constituting the entire open reading frame of OMP21 is illustrated in Example Section 8 at pages 57-60. Thus, the specification discloses and, in fact, presents an actual reduction to practice of an isolated nucleic acid which constitutes an entire open reading encoding OMP21 protein comprising the amino acid sequence of SEQ ID NO.: 7. A person skilled in the art would readily envision all the nucleic acids degenerate to SEQ ID NO.: 7 by using a genetic code table. Hence, one skilled in the art would conclude that Applicants were in possession of the subject matter of Claim 9 (and all claims dependent thereon) based on the specification and the general knowledge of the art. This is all that is required to meet the description requirements. See, e.g. The Guidelines for Examination of Patent Applications Under 35 U.S.C. §112, ¶1 "Written Description" Requirement, 66 Fed. Reg. 1099, Jan. 5, 2001 at FN. 57 which reads:

> For example, in the molecular biology arts, if an applicant disclosed an amino acid sequence, it would be unnecessary to provide an explicit disclosure of nucleic acid sequences that encoded the amino acid sequence. Since the genetic code is widely known, a disclosure of an amino acid sequence would provide sufficient information such that one would accept that an applicant was in possession of the full genus of nucleic acids encoding a given amino acid sequence, but not necessarily any particular species.

As detailed above, the present application provides not only an amino acid sequence of OMP21 but also an example of a full length nucleic acid which is an open reading frame encoding OMP21.

As amended, Claim 11 (and Claims 13, 16, 20, 71-73, 75-77 to the extent dependent thereon) and new Claim 79 recite an isolated nucleic acid encoding "an OMP21 protein of a *Moraxella catarrhalis* strain." Further these claims recite that the nucleic acid molecule encodes a polypeptide that elicits an immune response to *M. catarrhalis* when administered to an animal.

Attention is directed to the teaching of the application as a whole, to the definition of OMP21 at page 9, lines 16-24, which states that the term "OMP21" includes the protein obtainable from the outer membrane protein of *M. catarrhalis,* and obtainable from "any source by any means including chemical synthesis and recombinant means"; to Section 5.2 at pages 16-23, in particular at page 22, lines 16-24, which teaches that OMP21 can be produced in gene expression systems or can be chemically synthesized by methods known in the art; to Section 5.7 entitled "Nucleic Acid Encoding OMP21" at pages 36-46 discussed above; and Section 5.8 entitled "Recombinant Production of OMP21" which teaches methods for expressing the nucleic acids encoding OMP21 of *M. catarrhalis* in any recombinant expression systems known to those skilled in the art. Further attention is directed to the Examples presented in Sections 6, 8 and 11. In light of the detailed teaching of the specification and the illustrative examples, it is submitted that a person skilled in the art would readily envision all the nucleic acids encoding OMP21 of *Moraxella catarrhalis.* Thus, the specification fully describes the subject matter of claims 11 and 79 and all the description requirements are met.

New Claim 80 recites an isolated nucleic acid encoding an OMP21 wherein the nucleic acid comprises (a) SEQ ID NO.: 6; or (b) encodes amino acid of SEQ ID NO. 7 or (c) hybridizes to the nucleic acid of part a or b under specifically recited conditions and encodes a polypeptide which, when administered to an animal, elicits an immune response to

*M catarrhalis*. The subject matter of parts a and b of this claim is fully described in the specification as discussed above with respect to Claims 9 and 81. Further attention is directed to the teaching of the specification at page 19, line 25 through page 26, line 18 which clearly teaches that OMP21 polypeptides of the invention elicit an immune response to *M. catarrhalis* when administered to an animal. As taught throughout the specification, the nucleic acids of the invention encode the OMP21 polypeptide. The subject matter of part c of this claim is fully described in the specification, e.g., at page 38, lines 28-30 which teaches the specifically recited hybridization conditions and as discussed above with respect to Claims 9 and 81. Hence, one skilled in the art would conclude that Applicants were in possession of the subject matter of Claim 9 (and all claims dependent thereon) based on the specification and the general knowledge of the art.

With respect to Claim 78, attention is directed to the clear teaching of the specification at page 4, line 24 through page 5, line 3; at page 16, line 27 through page 17, line 14, particularly at page 16, line 31, and at page 19, lines 28-33. Claim 78 recites an isolated nucleic acid encoding a fragment of OMP21 of at least 10 amino acids and having an antigenic epitope of the amino acid sequence of SEQ ID NO.: 7, i.e., the full length of OMP21 protein. The subject matter of Claim 78 is fully described in the specification, e.g., at page 16, line 27 through page 17, line 14 which teaches that preferred OMP21 derived polypeptides encompass fragments of OMP21 of at least 10 amino acids and at page 39, lines 11-22 which teaches that the nucleic acids of the invention encode OMP21 derived polypeptides including fragments or portions thereof as described in Section 5.2 in combination with the teaching of the specification in Section 5.4 at pages 19, line 25 through page 20, line 18 which teaches that the fragments of OMP21 are "immunologically cross-reactive with wild-type OMP21" and that such fragments can be identified by several

methods. More particularly, the specification details methods to identify OMP21 derived polypeptides including fragments that bind to antibodies against OMP21 contained in intact *M. catarrhalis* cells, i.e., contain an antigenic epitope of OMP21. In light of such clear teaching, it is submitted that one skilled in the art would conclude that Applicants were in possession of the subject matter of Claim 78 at the time the application was filed. Thus, this rejection must be withdrawn.

In light of the above, this rejection of Claims 9, 11, 13, 16, 20 and 71-78 based on alleged lack of written description must be withdrawn.

Claims 9, 11-13, 16, 20 and 71-78 are rejected under Section 112, 1st paragraph as allegedly non-enabled. The Office Action indicates that the specification enables: an isolated nucleic acid molecule encoding an OMP21 isolated from *Moraxella catarrhalis* that has a molecular weight of about 16kD to about 20kD as determined by "non-reducing" SDS-PAGE using trypsin inhibitor and carbonic anhydrase as 21.5 kD and 31kD molecular weight standards, respectively, comprising a nucleic acid sequence 1) encoding SEQ ID NO.: 1 or 7; 2) that is the complement of 1); 3) selected from the group consisting of SEQ ID NO.: 2-6 and 8-14; 4) which hybridizes at 68°C in 0.5M $NaHOP_4$ (pH7.2)/1 mM EDTA/7%SDS to any one of the sequences of 1), 2) or 3); 5) which is at least 70% identical to SEQ ID NO.: 6; and 6) which is at least 70% identical to the complement of SEQ ID NO.: 6. The Office Action, however, alleges that only nucleic acids encoding an OMP21 protein isolated from *Moraxella catarrhalis* are enabled because the "only enabled use for the instant invention is to detect *M. catarrhalis*". Further, the Office Action alleges that "nucleic acids comprising non-natural sequences such as those that introduce mutations or restriction sites (SEQ ID NO.: 15-20)" which do not "encode the OMP21 of *M. catarrhalis*" are not enabled because "they cannot be used to detect the naturally occurring OMP21 of *M. catarrhalis*".

Attorneys for Applicants emphatically disagree and submit that the Office Action overlooks the clear teaching of the specification which demonstrates that the claimed nucleic acids have a number of uses in addition to use to detect *M. catarrhalis*. In particular, attention is directed to the teaching of the specification in Section 5.9 entitled "Applications" at pages 50-51. More particularly, attention is directed to the teaching at page 50, lines 21-32, which presents illustrative uses of the nucleic acids. Most particularly, after teaching that the nucleic acids can be used to detect or diagnose *M. catarrhalis* infection, the specification teaches that: "The DNA and RNA can also be used to identify other bacteria that might encode a polypeptide related to the *M. catarrhalis* OMP21". Further attention is directed to the specification in Sections 5.7 and 5.8. These sections provide, in detail, the nucleic acids encoding OMP21 of *M. catarrhalis* as well as nucleic acids hybridizable to same using any of a variety of hybridization conditions as well as methods to recombinantly produce the nucleic acids. Given the detailed teaching of the specification, one skilled in the art would certainly be able to make and use the subject matter of Claims 71-73 and 75-76.

A patent applicant's specification which contains a teaching of how to make and use the invention must be taken as enabling unless there is reason to doubt the objective truth of the teachings which must be relied on for enabling support. In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971); In re Brana, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995).

Where a disclosure provides considerable direction and guidance on how to practice the invention, and where, at the time of application, the skill in the art was quite high and the methods needed to practice the invention well known, a conclusion of enablement should be made. In re Wands, 858 F.2d 731, 740, 8 U.S.P.Q.2d. 1400, 1406 (Fed. Cir. 1988). Here, the specification provides a reasonable amount of guidance and direction so that a

skilled artisan could make and use the isolated nucleic acids encoding OMP21 for a number of uses.

Claims 9 and 11 are alleged to be enabled only for nucleic acid encoding a protein of the recited molecular weight as determined in "non-reducing" SDS-PAGE.

Attorneys for Applicants respectfully do not agree and submit that this allegation is factually incorrect. While not agreeing with this rejection, amended Claim 11 and new Claim 79 recite that the molecular weight is determined using "reducing" SDS-PAGE. Attention is directed to the description of Figure 2 at page 12, lines 3-21, also page 14, lines 10-24 and Example Section 6.2.2 at page 55. Hence, this rejection is avoided.

Claims 16, 76 and 77 are alleged to be enabled only for an "isolated" transformed cell.

In response, Claims 16, 76 and 77 are amended to recite and "isolated" transformed cell. Hence, this rejection is avoided.

Claims 71-73, 75 and 76 are alleged to be non-enabled because the specification is asserted not to enable "use of the nucleic acids fused to ... an affinity purification sequence".

Attorneys for Applicants respectfully, but emphatically disagree. Claims 71-73 and 75-76 are directed to the nucleic acids of Claim 9 or Claim 11 further comprising a heterologous sequence, i.e., encoding an OMP21 chimeric protein.

Attention is directed to the detailed description of the specification at Sections 5.7 and 5.8 at pages 36-50 which describes the nucleic acids encoding OMP21 and the use of the nucleic acids to recombinantly produce OMP21 as well as chimeric proteins comprising OMP21. In particular, attention is directed to the specification at page 47, line 36 through page 48, line 3 which teaches that the nucleic acids encoding OMP21 can be fused to a

heterologous protein, e.g. to an affinity purification peptide, so that a chimeric OMP21 fusion protein is expressed. Attention is further directed to Example 9 at pages 60-61 of the specification. As specifically exemplified therein, the nucleic acid comprising the open reading frame encoding OMP21 was modified at the 5′ end to change the lysine to an alanine and at the 3′ end to add a stretch of six histidines, i.e., an affinity purification peptide. The construction of a vector designated pOMP21X expressing nucleic acid encoding OMP21 modified at the 5′ and 3′ ends and expressing OMP21 fused to an affinity purification peptide is thus fully exemplified. Further, as taught in Section 9.2 at page 61, *E.coli* containing plasmid pOMP21X were cultured and OMP21 was obtained from the culture.

Finally, as indicated at page 66, lines 1-12, *E.coli* ToP10 F′ containing plasmid OMP21X was deposited in accord with Budapest Treaty requirements with the ATCC and will be available to the public upon issuance of a patent. Hence, an illustrative example of the claimed subject matter will be available to those skilled in the art. Accordingly, the subject matter of Claims 71-73 as well as claims 75-78 is fully enabled by the present application. Thus, this rejection must be withdrawn.

Claim 78 is alleged to be non-enabled with respect to a fragment comprising an antigenic epitope of SEQ ID NO.: 7.

Attorneys for Applicants respectfully, but emphatically disagree and submit that one skilled in the art, at the time the invention was made, surely would have been able to make and use the subject matter of Claim 78. Attention is directed to the teaching of the application at page 4, line 24 through page 5, line 3, at page 16, line 27 through page 17, line 14 and at page 19, line 25 through page 20, line 18. At page 4, the specification teaches that preferred nucleic acid sequences encode the OMP21 of SEQ ID NO.: 1 or 7 or fragments thereof. At page 16, line 31, the specification teaches that preferred OMP21 derived

polypeptides encompass fragments of at least 10 amino acids. At pages 19-20, the specification teaches that preferred OMP21 fragments, encoded by the nucleic acids, are immunogenic. Further, the specification at page 19, line 34 through page 20, line 18, describes two different methods to determine whether an OMP21 fragment has an antigenic epitope of OMP21. Finally, as discussed, in detail above, the specification provides the full length nucleotide sequence of the open reading frame of the molecule encoding OMP21, i.e, SEQ ID NO.: 7. In light of such teaching, it is clear, one skilled in the art would be able to make and use the nucleic acids of Claim 78 encoding a fragment of OMP21 and having an antigenic epitope of SEQ ID NO.: 7. Some experimentation would be necessary; however such experimentation would not be undue.

Thus, this rejection must be withdrawn.

Claim 81 is added to recite an isolated nucleic acid encoding a fragment of OMP21, said fragment comprising SEQ ID NO.: 1. As taught in the specification, at page 25, lines 11-22 and demonstrated in Examples 6 at pages 51-56, the OMP21 fragment comprising SEQ ID NO.: 1 is the N-terminal portion of the OMP21 molecule and the presence of such molecule is indicative of the presence of Moraxella cells. Thus, this claim is fully enabled and is in form for allowance.

Claims 9, 11, 13, 16, 20 and 71-77 are rejected under Section 112, 2nd paragraph as indefinite with regard to "apparent" molecular weight.

Although Attorneys for Applicants do not agree, simply to advance prosecution, the claims have been amended to avoid the terms deemed objectionable. Hence, this rejection is avoided.

**Conclusion**

In view of the amendments herein, the evidence presented in the Jackson Declaration regarding deposit and the remarks above, it is submitted that all outstanding objections and rejections have been avoided or overcome. Further, it is submitted that all the claims are in form for allowance. Early action to that end is requested. If any issues remain, it is requested that the undersigned be contacted at 212-790-2296.

Respectfully submitted,

Date March 13, 2002

Geraldine Frans Bald 31,232

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*Appendix A*

***Marked-Up Version of the Specification***
***Application No: 09/164,714***

**[Addition indicated by underlining and deletion indicated by square brackets]**

On page 12, beginning at line 22, replace the two paragraphs beginning "Figure 3...49143", with the following:

Figure 3. Determined nucleic acid sequence of OMP21 from *M. catarrhalis* strain 49143 SEQ ID NO.: 6.

Figure 4. Deduced Amino Acid Sequence of OMP21 from *M. catarrhalis* strain 49143 SEQ ID NO.: 7.

At page 25, replace the paragraph beginning "In other embodiments", at line 1, with the following:

In other embodiments, a peptide fragment of OMP21 is used as a n immunogen. Preferably, a peptide fragment of purified OMP21 or a chemically synthesized peptide fragment of OMP21 is used. The peptides may be produced by protease digestion, chemical cleavage of isolated or purified OMP21 or chemical synthesis and then may be isolated or purified. Such isolated or purified peptides can be used directly as immunogens. In particular embodiments, useful peptide fragments include but are not limited to those having the sequence AISYGNSADAQPYVGAKIGQVDAKQINGKNTAYGIYAGYN (SEQ ID NO.: 1) or any portion thereof that is 6 or more amino acids in length. In an another embodiment, the peptide has the sequence as shown in Figure [3] 4 (SEQ ID NO.: 7).

At pages 52-53, replace the paragraph at page 52, line 30 beginning "Antiserum to OMP21..." with the following:

Antiserum to OMP21 were prepared by resolving OMP21 polypeptide from OG extracts of *M. catarrhalis* strain ATCC 49143 in a DEAE SEPHAROSE™ ion exchange chromatography column. The fraction containing OMP21 was injected into a rabbit to generate antiserum to OMP21 polypeptide. In addition, affinity purified antibody was

prepared by injecting rabbits with blebs from *Moraxella catarrhalis* and purified using a cyanogen bromide activated agarose gel with immobilized OMP21. The gel was reacted with the antiserum and non-reactive antibodies and proteins were washed from the gel. Reactive antibodies were eluted from the gel using 100 mM glycine, pH2.5. The eluted antibodies were washed with PBS and concentrated. The concentrate was further purified by reacting with OMP21-deletion mutants of *M. catarrhalis*. The antiserum was analyzed by Western blots as described in Section 6.1.4., examined for complement-mediated cytotoxic activity against *M. catarrhalis* as described in Section 7 and inhibition of nasopharyngeal binding as described in Section [10] 13 (*infra*).

*Appendix B*

***U.S. Application Serial No. 09/164,714***
***Marked-Up version of claims***

[Addition indicated by underlining and deletion indicated by brackets]

9. (Twice Amended) An isolated nucleic acid molecule encoding an OMP21 protein wherein said OMP21 protein [has an apparent molecular weight of about 16 kD to about 20 kD as determined by SDS-PAGE using trypsin inhibitor and carbonic anhydrase, respectively, as 21.5 kD and 31 kD molecular weight standards and] comprises the amino acid sequence of SEQ ID NO: 7, or a complement of said nucleic acid molecule.

11. (Twice Amended) An isolated nucleic acid molecule encoding OMP21 protein [obtainable from] of a [*M.*] *Moraxella catarrhalis* strain, said OMP21 protein having molecular weight of about 16 kD to about 20 kD as determined by reducing SDS-PAGE, using trypsin inhibitor and carbonic anhydrase, respectively, as 21.5 kD and 31 kD molecular weight standards and wherein said nucleic acid molecule comprises a sequence selected from the group consisting of:

a) a nucleic acid sequence of any of SEQ ID NO: 2-6 and 8-14[20];

b) a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 1 or 7; and

c) a nucleic acid sequence which hybridizes at 68 degrees C in 0.5M NaHPO4 (pH7.2)/1 mM EDTA/ 7% SDS to any one of the sequences of a) or b); [and

d) a nucleic acid sequence which is at least 70% identical to the sequence of SEQ ID NO. 6 when identity is determined using the BLASTN algorithm, said] and said [sequence] nucleic acid molecule encoding a polypeptide that elicits an immune response to [*M.*] *Moraxella catarrhalis* when administered to an animal; or a complement of said nucleic acid molecule.

16. (Twice amended) [A] An isolated host cell transformed with the vector of Claim 13.



C

76. (Amended) [A] An isolated host cell transformed with the expression vector of Claim 75.

77. (Amended) [A] An isolated host cell transformed with the expression vector of Claim 20.



C